Field Cancer and Multiple SCC: Molecular Insights and Clinical Management

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The Problem: Multiple lesions in the field

Only 1 SCC, but numerous AK pose significant risk of subsequent cancer

SCC in situ (1st skin cancer)

AK in a sun damaged “field” of skin are analogous to weeds in a field of cultivated plants
The Problem: Multiple SCC

Many SCC and AK

SCC 1 year ago

SCC >1 year ago

Few AK, but 2 SCC within 6 months

SCC 6 months ago

The Problem: Recurrent Lesions

Two separate SCC
Treated with Mohs surgery

SCC in situ

2 years after Mohs surgery, both lesions SCC in situ
The Problem: Recurrent Lesions

Two separate SCC
Treated with Mohs surgery

2.25 years after first surgery.
All cancer excised. Are we done?

The Problem: Multiple Lesions
On the Legs

8 prior SCC on legs
34 prior SCC on legs
4 prior SCC on legs
Multiple SCC Associated with Poor Prognosis

1. **Increased risk of subsequent SCC**
   - After first SCC, 42% subsequent SCC within 5 years
   - After second or later SCC, 72% subsequent SCC within 5 years
     (Wehner, M.R, et al. *JAMA Dermatology* 2015; v151:p382)

1. **Increased risk of SCC progression**
   - Patients with 2-9 SCC: 2X risk of recurrence, 2.5X risk of nodal metastasis
   - Patients with >10 SCC: 12X risk of recurrence, 11X risk of nodal metastasis

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The Problem: Progressive Disease

Man in late 80s, >10 prior SCC/BCC

12 month period:
- 8 new SCC
- 7 new BCC

Rapidly enlarging neck mass
Metastatic SCC
Treated with surgery and radiation
Died 18 months later
Proposed the concept of “field cancerization”

- An area of epithelium is altered by a **regional carcinogenic effect**, leading to irreversible changes that eventually manifest in cancer
- Oral (and cutaneous) SCC arises from **multifocal areas** of precancerous change
- “Recurrence” after excision may represent **new primary cancer development**

Review of 783 cases of oral SCC

- 11% of cases had multiple primary lesions (grossly)
- In all cases, adjacent clinically benign mucosa was microscopically abnormal
  - Dyskeratosis and **separate islands** of SCC in situ or invasive SCC

Field Cancer Detection with Optical Coherence Tomography (OCT) in 2016

- Assessed clinically-diagnosed AK **AND** adjacent normal skin with OCT and biopsy
- 22 of 28 (79%) of clinically-normal skin had histopathologic evidence of AK/SCC
- 73% of these subclinical lesions were detectable with FD-OCT (Fourier-domain optical coherence tomography)

Clinical Definition of Field Cancer?

“I know it when I see it.”
- US Supreme Court Justice Potter Stewart, 1964

Working definition = 3 features
• defined region of skin
• multiple AK
• at least 1 SCC

Patients with heavy AK burden without SCC may also benefit from field therapy.

Multi-step Tumorigenesis

- Cancer is caused by the accumulation of DNA mutations that promote unrestrained growth

First mutation (e.g., loss of tumor suppressor) → Actinic keratosis → Hyperplastic actinic keratosis → Squamous cell carcinoma

Step-wise progression through precursor lesions

Hypotheses:
1. Burden of precursor lesions determines risk of carcinoma
   ✓ YES: AK strongly associated with SCC
2. Treatment of precursor lesions decreases incidence of carcinoma
Genetic Drivers of Cutaneous SCC

- Genome-wide sequencing has identified recurrent driver mutations in SCC
- Cutaneous SCC (and BCC) has highest mutation burden of any human cancer

<table>
<thead>
<tr>
<th>SCC tumors sequenced</th>
<th>Gene Mutation Frequency</th>
<th>Reference</th>
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<tbody>
<tr>
<td></td>
<td><strong>TP53</strong></td>
<td><strong>NOTCH1</strong></td>
</tr>
<tr>
<td>39</td>
<td>95%</td>
<td>59%</td>
</tr>
<tr>
<td>11</td>
<td>91%</td>
<td>75%</td>
</tr>
<tr>
<td>20</td>
<td>65%</td>
<td>40%</td>
</tr>
<tr>
<td>100</td>
<td>42%</td>
<td>54%</td>
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- **TP53** is the gene encoding the p53 tumor suppressor protein, often called the “guardian of the genome”
- **TP53** mutations may provide a genetic mark of field cancer

Characteristic UV Mutations are Present in Actinic Keratoses and Sun-Exposed Normal Skin

- Majority of actinic keratoses (60%) harbor **TP53** mutations
- 69% are UVB signature mutations (C→T)


- **TP53** mutations are present in histologically normal skin
- Burden of mutated **TP53** is 11x greater in sun-exposed skin

  Jonason, et al., *Proc Natl Acad Sci* 93:14025; 1996
TP53 Mutant Clones Expand with UVB Exposure

- Mutant TP53 cells can be identified by antibody staining as clusters or clones
- Number of clusters correlates with skin cancer risk


- Mice exposed to daily UVB develop TP53 mutant clones
- Clones increase in number and size only during UVB exposure

Zhang, et al., PNAS 98:13948; 2001

Stopping UVB exposure decreased the number of pre-malignant lesions

High Burden of Carcinogenic Mutations in Normal Skin

- DNA sequencing of normal eyelid skin
- Up to 32% of skin cells had carcinogenic mutations
- Frequent mutations in TP53 and Notch1
- Most common mutation was UV-signature (C→T) mutation
- Sun-exposed skin is “a patchwork of thousands of evolving clones”

Sunblock Use Decreases AK (and Field Damage)

- Australian trial, 588 patients with 1-30 AK
  - randomized to SPF 17 sunblock vs vehicle, instructed to apply 4.5 ml daily
  - 7 month follow up over summer months
- Sunscreen = 28% reduction in new AK
  - and 39% increased regression of old AK
- Patients using greatest amount of sunblock had greatest protection
  - recommended amount: 950g (33 ounces)

For actinic field damage, regular sunblock use is effective even in patients with established disease.

Sunblock Use Decreases SCC

- Australian population-based trial of 1621 patients
  - low risk population, only 27% had history of skin cancer
  - randomized to SPF 16 broad-spectrum sunblock daily vs “discretionary use”
  - follow up every 3 months for 4 years
- Sunscreen = 39% reduction in new SCC (28 vs. 48 SCC, p < 0.05)
  - sunscreen had no effect on BCC


- Additional 8 year follow up of same patients
  - sunscreen use was discretionary in follow up period
  - Sunscreen = 41% reduction in new SCC (81 vs 142 SCC, p < 0.05)

Summary: Field Cancer Paradigm

1. SCC is caused by the accumulation of genetic mutations
2. Visible (actinic keratosis) and invisible (mutant clone) lesions precede SCC development
3. UVB induces mutations, and mutant clones expand under continuing UV exposure
4. A sun-damaged field has thousands of mutant clones with the potential to develop into cancer
5. Lesion directed therapy alone does not address these pre-malignant clones
Field-Directed Therapy

1. Sun protection
2. Topical therapy
   - 5-fluorouracil
   - Imiquimod
   - Ingenol mebutate
3. Photodynamic therapy
4. Systemic therapy
   - Acitretin
   - Nicotinamide
5. Combination therapy

Field-Directed Therapy Toolkit

<table>
<thead>
<tr>
<th></th>
<th>Efficacy: AK treatment</th>
<th>Efficacy: SCC Prevention</th>
</tr>
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<tbody>
<tr>
<td>Topicals: 5-FU, imiquimod, ingenol</td>
<td>High</td>
<td>No data</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>High</td>
<td>Moderate?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(uncontrolled study 80% reduction with cyclic PDT)</td>
</tr>
<tr>
<td>Systemic acitretin</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Systemic nicotinamide</td>
<td>Low</td>
<td>Low</td>
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PDT Treatment of Field Cancer

1. Prospective study of 12 transplant patients treated with cyclic PDT to arms (or legs) every 4-8 weeks for 2 years

<table>
<thead>
<tr>
<th></th>
<th>12 months before PDT</th>
<th>1st year of PDT</th>
<th>2nd year of PDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of SCC</td>
<td>20</td>
<td>4 (79% reduction)</td>
<td>1 (95% reduction)</td>
</tr>
</tbody>
</table>


2. Trial of 40 transplant patients randomized to receive PDT one arm only: over 2 year follow up, 15 SCC in PDT arm and 10 SCC in control arm


Systemic Field Therapy: Acitretin

- Oral retinoids (e.g., acitretin and isotretinoin) bind to retinoic acid receptors in keratinocytes to modulate proliferation, differentiation, lipid production, and inflammatory signals
- Retinoids normalize epidermal differentiation
- Acitretin is FDA-approved for psoriasis, not AK or SCC

- **Pregnancy category X**
  - Acitretin half-life 2-3 days
  - With ethanol exposure, acitretin → etretinate, half life >3 months

- Predictable dose-dependent side effects of xerosis and mucositis in most patients
- Hair thinning, nail thinning, muscle and joint pain also common
- Contraindicated with severe renal or hepatic impairment
- Up to ⅓ of patients develop elevated triglyceride, cholesterol, or liver function test levels (mild leukopenia is rare)
Systemic Field Therapy: Acitretin

Prospective trial of 44 renal transplant recipients with multiple keratotic lesions, half had prior skin cancer (high risk cohort).

- Randomized to acitretin 30mg daily or placebo for 6 months
- 88% reduction in SCC with acitretin
- Greatest reduction in patients with prior SCC
- “Rebound” SCC in 6 month follow up after acitretin stopped


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Systemic Field Therapy: Acitretin

Prospective trial of 70 non-transplant patients with history of ≥2 BCC/SCC (lower risk cohort)

- Randomized to acitretin 25mg/day, five days/week or placebo for 2 years
- Did not clearly differentiate BCC vs SCC risk
- Incidence of new BCC/SCC not significantly reduced with acitretin
- 56% reduction in total BCC/SCC with acitretin (119 vs. 52, p = 0.03)

Potential Indications for Acitretin (not FDA-approved)

1. Overwhelming SCC burden at presentation
   • Acitretin = more effective SCC suppression than other field therapies
   • Systemic drug = treatment of many fields simultaneously

2. High rate of lower leg SCC
   • Other field therapies are less effective on distal extremities than on head/neck

3. Persistent SCC development despite other field therapies
   • Moving up the therapeutic ladder

Protocol for Oral Acitretin Therapy

**Initiation**

- Not recommended in patients of reproductive potential
- Advise on expected xerosis, dry eyes, dry lips, counsel on emollients, lip balms, lubricating eye drops
- Advise on potential muscle aches and hair thinning
- Baseline labs: cbc, BUN/creatinine, LFTs, fasting lipid panel
- Counsel about ethanol avoidance

**Titration**

- Start low and titrate upward to effect
- Increase dose every 2-6 months as needed/tolerated
  
  10mg every other day → 10mg daily → 25mg daily
- Repeat labs monthly during titration, Q3 months when stable
Acitretin for Multiple Leg SCC

- Woman in mid 70s with history of dermatitis and prurigo nodules
- Referred for evaluation/treatment of multiple SCC on lower legs
- 5 separate SCC were diagnosed by biopsy over a 3 month period

Acitretin for Multiple Leg SCC

- After 18 months on acitretin 25mg daily
- 3 other SCC treated with biopsy and cautery in first 6 months of therapy
- No other SCC during treatment, or after cessation (18 months off therapy to date)
Systemic Field Therapy: Nicotinamide

- Nicotinamide (aka niacinamide) is the amide form of niacin (vitamin B3), available as OTC supplement
- Unlike oral niacin, nicotinamide is NOT associated with flushing or lipid-lowering effects
- Nicotinamide is precursor for NAD (nicotinamide adenine dinucleotide), a critical cofactor for cellular energy production and DNA repair
- Preclinical studies suggest nicotinamide minimizes UV-induced immune suppression and carcinogenesis

Two combined phase 2 trials:
- 74 patients randomized to nicotinamide 500mg once or twice daily versus placebo
- At 4 months, 29-35% reduction in AK (more with twice daily dose) \( p < 0.001 \)

Systemic Field Therapy: Nicotinamide

- Phase 3 trial of 386 patients with \( \geq 2 \) skin cancer, randomized to 500mg nicotinamide bid or placebo for 12 months

23% decrease in NMSC while on nicotinamide
No adverse events attributed to drug

### Summary: Field Directed Therapy

<table>
<thead>
<tr>
<th>Field Treatment</th>
<th>Advantages</th>
<th>Drawbacks</th>
<th>FDA Approved?</th>
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<tbody>
<tr>
<td><strong>5-fluorouracil</strong></td>
<td>Predictable response, generic available</td>
<td>4 week treatment</td>
<td>Only for AK</td>
</tr>
<tr>
<td><strong>Imiquimod</strong></td>
<td></td>
<td>Unpredictable, &gt;4 week treatment</td>
<td>Only for AK</td>
</tr>
<tr>
<td><strong>Ingenol mebutate</strong></td>
<td>Short 2-3 day treatment</td>
<td>Unpredictable, may be costly</td>
<td>Only for AK</td>
</tr>
<tr>
<td><strong>PDT</strong></td>
<td>Single day treatment, ensured compliance</td>
<td>Specialized equipment, time-intensive (for MD)</td>
<td>Only for AK</td>
</tr>
<tr>
<td><strong>Acitretin</strong></td>
<td>Potent reduction in SCC</td>
<td>Laboratory monitoring, side effects, potential rebound phenomenon</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Nicotinamide</strong></td>
<td>Well-tolerated OTC supplement</td>
<td>Minimal SCC reduction, minimal clinical experience</td>
<td>NO</td>
</tr>
</tbody>
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### Risk Assessment & Treatment Selection

<table>
<thead>
<tr>
<th>Field Cancer Risk</th>
<th>Clinical Features</th>
<th>General Management</th>
<th>Primary Field Treatment</th>
<th>Secondary Treatment</th>
</tr>
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<tbody>
<tr>
<td><strong>LOW</strong></td>
<td>10 AK in field OR Immunosuppressed &amp; &gt;1 AK</td>
<td>UV protection and lesion-directed therapy as indicated</td>
<td>Topical or PDT field therapy as needed</td>
<td></td>
</tr>
<tr>
<td><strong>MODERATE</strong></td>
<td>2-3 SCC/year OR Immunosupp. &amp; 1 SCC/year</td>
<td></td>
<td>Cyclic topical or PDT field therapy</td>
<td>Consider acitretin (esp. lower leg)</td>
</tr>
<tr>
<td><strong>HIGH</strong></td>
<td>&gt;3 SCC/year OR 10 lifetime SCC OR Immunosupp. &amp; &gt;1-2 SCC/year</td>
<td></td>
<td>Acitretin</td>
<td>Cyclic field therapy AND aggressive lesion control</td>
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